Physician Prescribing Information

1. NAME OF THE MEDICINAL PRODUCT

FIRDAPSE

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains amifampridine phosphate equivalent to 10 mg of amifampridine.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet.
White, round tablet, flat-faced on one side and scored on the other side.
The tablets can be divided into equal halves.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Symptomatic treatment of Lambert-Eaton myasthenic syndrome (LEMS) in adults.

4.2 Posology and method of administration

Treatment should be initiated under supervision of a physician experienced in the treatment of the disease.

<u>Posology</u>

FIRDAPSE should be given in divided doses, three or four times a day. The recommended starting dose is 15 mg amifampridine a day, which can be increased in 5 mg increments every 4 to 5 days, to a maximum of 60 mg per day. No single dose should exceed 20 mg.

Tablets are to be taken with food. Please see section 5.2 for further information about bioavailability of amifampridine in the fed and fasted state.

If treatment is discontinued, patients may experience some of the symptoms of LEMS.

Renal or hepatic impairment

FIRDAPSE should be used with caution in patients with renal or hepatic impairment. A starting dose of 5 mg amifampridine (half tablet) once per day is recommended in patients with moderate or severe impairment of renal or hepatic function. For patients with mild impairment of renal or hepatic function, a starting dose of 10 mg amifampridine (5 mg twice a day) per day is recommended. Patients should be titrated more slowly than those without renal or hepatic impairment with doses increased in 5 mg increments every 7 days. If any adverse reaction occurs, upward dose titration should be discontinued (see sections 4.4 and 5.2).

Paediatric population
The safety and efficacy of FIRDAPSE in children aged 0 to 17 years has not been established. No data are available.

Method of administration

For oral use only.

4.3 Contraindications

- Hypersensitivity to the active substance, or to any of the excipients listed in section 6.1
- Epilepsy
- Uncontrolled asthma
- Concomitant use with sultopride (see sections 4.5 and 5.1)
- Concomitant use with medicinal products with a narrow therapeutic window (see section 4.5)
- Concomitant use with medicinal products with a known potential to cause QTc prolongation
- In patients with congenital QT syndromes (see section 4.4)

4.4 Special warnings and precautions for use

Renal and hepatic impairment

The pharmacokinetics of amifampridine has been assessed in a single dose Phase I study in patients with renal impairment (see section 5.2).

No studies have been conducted in patients with hepatic impairment. In view of the risk of markedly increased exposure to medicinal product, patients with renal or hepatic impairment must be carefully monitored. The dose of amifampridine should be titrated more slowly in patients with renal and hepatic impairment than those with normal renal and hepatic function. Upward dose titration should be discontinued if any adverse reaction occurs (see section 4.2).

Seizures

Exposure to amifampridine is associated with an increased risk for epileptic seizures. The risk of seizures is dose-dependent and is increased in patients with risk factors which lower the epileptic threshold; including use in combination with other medicinal products known to lower the epileptic threshold (see section 4.5). In the event of a seizure, treatment should be discontinued.

Carcinogenicity risk

The use of amifampridine in patients with the non-paraneoplastic form of LEMS should only be commenced following a thorough assessment of the risk-benefit to the patient.

In a 2-year dietary carcinogenicity study, benign and malignant Schwannomas have been observed in rats treated with amifampridine (see section 5.3). Amifampridine was not genotoxic in a standard battery of *in vitro* and *in vivo* tests. The correlation between the use of amifampridine and the development of tumours in humans is unknown at this time.

Most Schwannomas are benign and asymptomatic. They can present in many locations, therefore the clinical presentation can be varied. A diagnosis of Schwannoma should be considered for patients who present with symptoms such as a mass that is painful on palpation or symptoms similar to a compressive neuropathy. Schwannomas are generally slow-growing and can exist for months to years without producing symptoms. The benefit of continuing treatment with amifampridine should be reviewed for any patient who develops a Schwannoma.

Amifampridine should be used with caution in patients with an increased risk of Schwannomas, such as patients with past medical history of such tumours, neurofibromatosis Type 2 or schwannomatosis

Cardiac effects

Clinical and electrocardiogram (ECG) monitoring are indicated at the initiation of the treatment and yearly thereafter. In case of signs and symptoms indicative of cardiac arrhythmias, ECG should be performed immediately.

Concomitant diseases

Patients must be told to inform any physician they consult that they are taking this medicinal product, since close monitoring of a concomitant disease, particularly asthma, may be necessary.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacokinetic interactions

Medicinal products eliminated through metabolism or active secretion
There are no data on the effects of amifampridine on the metabolism or active secretion of other medicinal products. Thus, special care should be taken in patients undergoing concomitant treatment with medicinal products eliminated through metabolism or active secretion. Monitoring is advised when possible. The dose of the concomitantly given medicinal product should be adjusted if necessary. Concomitant use of medicinal products with a narrow therapeutic window is contraindicated (see section 4.3).

Substances which are potent inhibitors of enzymes that metabolise medicinal products (see section 5.2)
Potent cytochrome P450 (CYP450) enzyme inhibitors e.g. cimetidine, ketoconazole are not likely to inhibit the metabolism of amifampridine by human N-acetyl-transferase enzymes (NATs) giving rise to increased amifampridine exposure. The results from the *in vitro* CYP450 inhibition study indicate amifampridine is unlikely to play a role in metabolic-based clinical drug-drug interactions related to inhibition of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4 metabolism of co-administered medicinal products. Regardless, patients should be closely monitored for adverse reactions when initiating treatment with a potent enzyme or renal transporter inhibitor. If treatment with a potent inhibitor is discontinued, patients should be monitored for efficacy as an increase of amifampridine dose may be necessary.

Substances which are potent inducers of enzymes that metabolise medicinal products (see section 5.2)
The results from *in vitro* studies suggest there is low potential for drug-drug interactions due to enzyme induction of CYP1A2, CYP2B6, and CYP3A4 enzymes by amifampridine.

Pharmacodynamic interactions

Based on the pharmacodynamic properties of amifampridine, the concomitant use with sultopride or other medicinal products known to cause QT prolongation (e.g., disopyramide, cisapride, domperidone, rifampicin and ketoconazole) is contraindicated as this combination may lead to an enhanced risk of ventricular tachycardia, notably torsade de pointes (see sections 4.3 and 5.1).

Combinations requiring precautions for use

Medicinal products known to lower the epileptic threshold
The concomitant use of amifampridine and substances known to lower the epileptic threshold may lead to an increased risk of seizures. The decision to administer proconvulsant or epileptic-threshold lowering substances concomitantly should be carefully considered in the light of the severity of the associated risks. These substances include most anti-depressants (tricyclic antidepressants, selective serotonin uptake inhibitors), neuroleptics (phenothiazines and butyrophenones), mefloquine, bupropion and tramadol (see sections 4.4 and 5.1).

Combinations to be taken into consideration

Medicinal products with atropinic effects
The concomitant use of amifampridine and medicinal products with atropinic effects may reduce the effect of both active substances and should be taken into consideration. Medicinal products with atropinic effects include tricyclic anti-depressants, most H1 atropinic anti-histamines, anticholinergic, anti-Parkinson medicinal products, atropinic antispasmodics, disopyramide, phenothiazine neuroleptics and clozapine.

Medicinal products with cholinergic effects
The concomitant use of amifampridine and medicinal products with cholinergic effects (e.g. direct or indirect cholinesterase inhibitors) may lead to an increased effect of both products and should be taken into consideration.

Non depolarising muscle relaxant acting medicinal products
The concomitant use of amifampridine and medicinal products with non-depolarising muscle relaxant effects (e.g. mivacurium, pipercurium) may lead to a decreased effect of both products and should be taken into consideration.

Depolarising muscle relaxant acting medicinal products
The concomitant use of amifampridine and medicinal products with depolarising muscle relaxant effects (e.g. suxamethonium) may lead to a decreased effect of both products and should be taken into consideration.

4.6 Fertility, pregnancy and lactation

Pregnancy

FIRDAPSE should not be used during pregnancy. Women of childbearing potential must use effective contraception during FIRDAPSE treatment. No adequate clinical data on exposed pregnancies are available for amifampridine. Amifampridine has shown no effect on embryo-foetal viability and development in rabbits; however, in rats, an increase in the number of mothers delivering still-born offspring was observed (see section 5.3).

Breast-feeding

It is unknown whether amifampridine is excreted in human breast milk. Available reproductive data in animals have shown presence of amifampridine in milk of breast-feeding mothers. Assessment of breast-feeding neo-natal animals showed no indication of adverse reactions when exposed to amifampridine through breast-milk. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from FIRDAPSE therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Fertility

Non-clinical safety data are available regarding the effects of amifampridine on reproductive function. No impairment of fertility has been observed in non-clinical studies with amifampridine (see section 5.3).

4.7 Effects on ability to drive and use machines

Due to adverse reactions such as drowsiness, dizziness, seizures and blurred vision, amifampridine may have minor or moderate influence on the ability to drive or use machines (see section 4.8).

Important information about some ingredients of the medicine
FIRDAPSE is gluten-free medicinal product. Do not use if you are allergic to any of the other ingredients of this medicine (see Section 6.1).

4.8 Undesirable effects

Summary of the safety profile

The most commonly reported adverse reactions are paraesthesias (such as peripheral and peribucal paraesthesias) and gastro-intestinal disorders (such as epigastralgia, diarrhoea, nausea and abdominal pain). The intensity and incidence of most adverse reactions is dose-dependent.

Table 1 below lists the adverse reactions reported with amifampridine.

Tabulated list of adverse reactions

Frequencies are defined as: Very common (≥ 1/10), Common (≥ 1/100 to < 1/10), Uncommon (≥ 1/1000 to < 1/100), Rare (≥ 1/10,000 to < 1/1,000), Very rare (< 1/10,000) and Unknown (cannot be estimated from available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Frequencies were estimated based on a clinical study to evaluate the effects of amifampridine on cardiac repolarization at a single dose of 30 mg or 60 mg in healthy volunteers.

Table 1: Adverse Reactions Reported with FIRDAPSE

MedDRA System organ class	MedDRA Preferred term	Frequency
Psychiatric disorders	Sleep disorders, anxiety	Unknown
Nervous system disorders	Convulsions, chorea, myoclonia drowsiness, weakness, fatigue, headache	Unknown
	Dizziness[1], hypoaesthesia[1], paraesthesia[1]	Very common
Eye disorders	Blurred vision	Unknown
Cardiac disorders	Cardiac rhythm disorders, palpitations	Unknown
Vascular disorders	Raynaud's syndrome	Unknown
	Cold extremities[1]	Common
Respiratory, thoracic and mediastinal disorders	Bronchial hypersecretion, asthma attack in asthmatic patients or patients with a history of asthma, cough	Unknown
Gastrointestinal disorders	Hypoaesthesia oral[1], paraesthesia oral[1], peripheral and peribucal paraesthesias, nausea[1]	Very common
	Abdominal pain	Common
	Diarrhoea, epigastralgia	Unknown
Hepatobiliary disorders	Elevated liver enzyme levels (transaminases)	Unknown
Skin and subcutaneous disorders	Hyperhidrosis[1], cold sweat[1]	Very common

[1] *Adverse reactions reported in a clinical study to evaluate the effects of amifampridine on cardiac repolarization at a single dose of 30 mg or 60 mg in healthy volunteers.*

<u>Reporting of suspected adverse reactions</u>

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il/

4.9 Overdose

There is little experience with overdose. The manifestations of acute overdose include vomiting and abdominal pain. Patient should discontinue the treatment in the event of overdose. No specific antidote is known. Supportive care should be given as clinically indicated, including close monitoring of vital signs.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: other nervous system drugs, ATC code: N07XX05.

<u>Mechanism of action</u>

Amifampridine blocks voltage-dependent potassium channels, thereby prolonging pre-synaptic cell membrane depolarisation. Prolonging the action potential enhances the transport of calcium into the nerve ending. The resulting increase in intra-cellular calcium concentrations facilitates exocytosis of acetylcholine-containing vesicles, which in turn enhances neuromuscular transmission.

It improves muscle strength and resting compound muscle action potential (CMAP) amplitudes with an overall weighted mean difference of 1.69 mV (95% CI 0.60 to 2.77).

Pharmacodynamic effects

The pharmacodynamic profile of amifampridine has been studied for a range of doses. A prospective, placebo-controlled, randomised study in 26 patients with Lambert-Eaton myasthenic syndrome (LEMS) reported clinical efficacy for amifampridine at the standard recommended maximum dose of 60 mg/day (Sanders *et al* 2000). Two further studies in a total of 57 patients with LEMS have reported data from higher doses of amifampridine. McEvoy *et al* 1989 reported data from a short-term study in 12 patients with LEMS, which demonstrated that administration of amifampridine at doses up to 100 mg/day for a period of 3 days was effective in treating the autonomic and motor symptoms of LEMS. Sanders *et al* 1998 presented data on efficacy and safety of amifampridine treatment at doses up to 100 mg/day in 45 patients with LEMS who were treated for an average of 31 months. Therefore, in exceptional circumstances higher doses up to a maximum of 80 mg/day may be of benefit when given with the appropriate safety monitoring. It is recommended that dose titration from 60 mg/day to 80 mg/day is performed in 5 mg increments every 7 days. Upward dose titration should be discontinued if any adverse reaction or ECG abnormality is observed.

The effect of a single dose of 30 mg or 60 mg of amifampridine phosphate was used to evaluate the pharmacokinetic-QTc relationship of amifampridine concentration on cardiac repolarization exposure in healthy volunteers. This evaluation was conducted in a Phase 1, double-blind, randomized, crossover study to define the ECG effects of amifampridine phosphate at these doses compared to placebo and moxifloxacin (a positive control) in healthy men and women who are slow acetylators (n=52). There was no effect of amifampridine phosphate on heart rate, atrioventricular conduction or cardiac depolarization as measured by the heart rate, PR and QRS interval durations. No subjects developed new clinically relevant ECG morphological changes following administration of amifampridine phosphate. No effect was observed of amifampridine phosphate on cardiac repolarization as assessed using the QTc interval.

Clinical efficacy and safety

A double-blind, placebo-controlled, randomized withdrawal Study to evaluate the efficacy and safety of amifampridine phosphate in Patients with LEMS was conduct in adult patients 18 years of age or older (n=26). The patients were maintained on a stable dose and frequency of amifampridine phosphate for at least 7 days prior to randomization. In this four-day study, patients were randomized (1:1) to amifampridine phosphate (at patient’s optimal dose) or placebo on Day 0. Baseline assessments were obtained on day 0. The primary endpoints were change from baseline (CFB) in Patient Global Impression (SGI) and Quantitative Myasthenia Gravis (QMG) score at Day 4. A secondary efficacy endpoint was the change from baseline at Day 4 in CGI-I score, which was determined by treating physicians. Patients were allowed to use stable doses of peripherally acting cholinesterase inhibitors or corticosteroids. Patients with recent use of immunomodulatory therapies (e.g., azathioprine, mycophenolate, cyclosporine), rituximab, intravenous immunoglobulin G, and plasmapheresis were excluded from the study. Patients had a median age of 55.5 years (range: 31 to 75 years) and 62% were female and 38% were male.

Following the 4 day double-blind discontinuation period, patients treated with amifampridine phosphate maintained muscle strength compared to patients treated with placebo who showed worsening of muscle strength. Observed mean difference in QMG Total and SGI change from baseline score between treatments were -6.54 (95% CI: -9.78, -3.29; p=0.0004) and 2.95 (95% CI: 1.53, 4.38; p=0.0003) respectively, both statistically significant in favour of amifampridine phosphate. In addition, CGI-I scores at day 4 as determined by physicians showed significant improvement in patients remaining on amifampridine phosphate compared to placebo (p=0.0020).

Summary of Changes in Primary and Secondary Efficacy Endpoints from Baseline

Assessment	Amifampridine (n=13)	Placebo (n=13)
QMG Scores[a]		
LS Mean[d]	0.00	6.54

LS Mean Diff (95% CI)	-6.54 (-9.78, -3.29)	
p-value[d]	0.0004	
SGI Scores[b]		
LS Mean[d]	-0.64	-3.59
LS Mean Diff (95% CI)	2.95 (1.53, 4.38)	
p-value[d]	0.0003	
CGI-I Scores[c]		
Mean (SD)	3.8 (0.80)	5.5 (1.27)
p-value[e]	0.0020	

a Total QMG score range 0 – 39, 13 items, 0-3 points on each test. The more points = worse symptoms.

b SGI is a 7-point scale which rates the global impression of the effects of study treatment (1=terrible to 7=delighted).

c CGI-I is a 7-point scale based on changes in symptoms, behaviour, and functional abilities (1=very much improved to 7=very much worse).

d CFB for QMG total score was modelled as the response, with fixed effects terms for treatment and QMG at Baseline.

e p-value based on the Wilcoxon Rank Sum Test for treatment differences.

5.2 Pharmacokinetic properties

Absorption

Orally administered amifampridine is rapidly absorbed in humans, reaching peak plasma concentrations by 0.6 to 1.3 hours (mean values).

In humans, the rate and extent of absorption of amifampridine is influenced by food (see Table 2). There was a decrease in C_{max} and AUC, and an increase in the time to reach maximum plasma concentrations when amifampridine phosphate was administered with food as compared to without food. A 2-fold increase in the time to reach C_{max} (T_{max}) was observed in the presence of food. Similarly C_{max} and $AUC_{0-\infty}$ were greater in the fasted state than in the fed state. Overall, food slowed and decreased the absorption of amifampridine with a lowering of exposure by C_{max} on average by ~44% and lowered exposure by AUC ~20%. based on geometric mean ratios (fed-to-fasted).

Apparent plasma terminal elimination half-life differences were 3-4 fold between subjects in the food effect study. Bioavailability is approximately 93-100% based on recoveries of unmetabolised amifampridine and a major 3-N-acetylated amifampridine metabolite in urine.

Table 2: PK Parameters for Amifampridine in Fed and Fasted Subjects Following Administration of a Single Oral Dose of Amifampridine Phosphate

Amifampridine 20 mg	**C_{max} (ng/ml) mean (S.D.), range**	**$AUC_{0-\infty}$ (ng·hr/ml) Mean (S.D.), range**	**T_{max} (hr) mean(S.D.), range**	**$t_{1/2}$ (hr) mean (S.D.), range**
Fasted (N=45)	59.1 (34.4), 16-137	117 (76.6), 22.1-271	0.637 (0.247), 0.25-1.5	2.5 (0.73), 1.23-4.31
Fed* (N=46)	40.6 (31.3), 2.81-132	109 (76.4), 9.66-292	1.31 (0.88), 0.5-4.0	2.28 (0.704), 0.822-3.78

* Eating a standardised high-fat meal

In a study of healthy volunteers, systemic exposure of amifampridine was notably influenced by the overall metabolic acetylation activity of NAT enzymes and NAT2 genotype. The NAT genes are highly polymorphic and result in phenotypes with variable acetylation activity rates ranging from slow to fast. In the healthy volunteer study, fast acetylators were defined by having a caffeine metabolite ratio >0.3 and slow acetylators with a caffeine metabolite ratio <0.2. There was significantly higher exposure to amifampridine in slow acetylators compared to fast acetylators. Statistically significant differences in amifampridine PK parameters C_{max}, $AUC_{0-\infty}$, $t_{1/2}$ and apparent clearance was observed between fast and slow acetylators at all dose levels. In this study, slow acetylators experienced more adverse reactions than the fast acetylators. The safety profile in this study is consistent with adverse reactions observed with patients on amifampridine.

Table 3: Mean PK Parameters of Amifampridine in Healthy Subjects after Single Oral Doses (5-30mg) in Slow and Fast Acetylator Phenotypes

Amifampridine Dose (mg)	**5**		**10**		**20**		**30**	
Subjects (N)	6	6	6	6	6	6	6	6
Acetylator Phenotype	Fast	Slow	Fast	Slow	Fast	Slow	Fast	Slow
Mean Amifampridine PK Parameters								
AUC_{0-t} (ng·hr/ml)	2.89	30.1	9.55	66.3	24.7	142	43.5	230
$AUC_{0-\infty}$ (ng·hr/ml)	3.57	32.1	11.1	68.9	26.2	146	45.2	234
C_{max} (ng/ml)	3.98	17.9	9.91	34.4	16.2	56.7	25.5	89.6
T_{max} (hr)	0.750	0.830	0.805	1.14	1.04	1.07	0.810	1.29
$t_{1/2}$ (hr)	0.603	2.22	1.21	2.60	1.23	2.93	1.65	3.11

The mean caffeine acetylator ratio for these 12 subjects receiving four escalating doses were 0.408 and 0.172 for fast and slow acetylators types respectively.

Distribution

Distribution of amifampridine was studied in the rat. Following oral administration of radiolabeled [^{14}C] amifampridine, radioactive material is rapidly absorbed from the gastrointestinal tract and widely distributed throughout the body. Concentrations in tissues are generally similar to or greater than concentrations in plasma, with the greatest concentration in organs of excretion (liver, kidney and the gastrointestinal tract) and some tissues of glandular function (lacrimal, salivary, mucous, pituitary and thyroid glands).

Biotransformation

In vitro and *in vivo* studies in humans indicate that amifampridine is metabolised to a single major 3-N-acetylated amifampridine metabolite.

Elimination

In humans, 93.2% to 100% of amifampridine is excreted into the urine within 24 hours after dosing as amifampridine (19%) and its 3-N-acetylated amifampridine metabolite (74.0% to 81.7%). The plasma elimination half-life is approximately 2.5 hours for the amifampridine and 4 hours for the 3-N-acetylated amifampridine metabolite.

The overall clearance of amifampridine is predominantly due to metabolism by N-acetylation and acetylator phenotype has a greater effect on an individual's metabolism and elimination of amifampridine than does elimination by renal function (See Table 4).

Renal impairment

Exposure of amifampridine was generally higher in subjects with renal impairment than in subjects with normal renal function; however, NAT2 phenotype had a greater effect on an individual's exposure to amifampridine than renal function status (See Table 4). Amifampridine exposure by $AUC_{0-\infty}$ was up to 2-fold higher in slow acetylators and up to 3-fold higher in fast acetylators with severe renal impairment compared to subjects with normal renal function. Exposure by C_{max} was marginally affected by renal impairment regardless of acetylation status.

In contrast, the 3-N-acetyl metabolite exposure levels were affected to a greater extent by renal impairment than those for amifampridine. The 3-N-acetyl metabolite exposure by $AUC_{0-\infty}$ was up to 6.8-fold higher in slow acetylators and up to 4-fold higher in fast acetylators with severe renal impairment compared to subjects with normal renal function. Exposure by C_{max} was only marginally affected by renal impairment regardless of acetylation status. Although the metabolite is inactive at potassium channels, potential off target effects due to accumulation are unknown.

Table 4: Mean PK Parameters of Amifampridine in Normal and Renal Impaired Subjects after Single Oral Dose Administration (10mg) in Slow and Fast Acetylator Phenotypes

Renal Status	Normal		Mild		Moderate		Severe	
Subjects (N)	4	4	4	4	4	4	4	4
NAT2 Phenotype	Fast	Slow	Fast	Slow	Fast	Slow	Fast	Slow
Mean Amifampridine PK Parameters								
$AUC_{0-\infty}$ (ng·h/ml)	10.7	59.1	16.1	81.3	14.3	126	32.8	119
C_{max} (ng/ml)	7.65	38.6	11.1	33.5	8.33	52.5	9.48	44.1
T_{max} (hr)	0.44	0.43	0.88	0.88	0.51	0.55	0.56	0.63
$t_{1/2}$ (hr)	1.63	2.71	1.86	2.95	1.72	3.89	1.64	3.17
Mean 3-N-acetyl Amifampridine PK Parameters								
$AUC_{0-\infty}$ (ng·h/ml)	872	594	1264	1307	2724	1451	3525	4014
C_{max} (ng/ml)	170	115	208	118	180	144	164	178
T_{max} (hr)	1.13	0.75	1.44	1.38	2.00	1.13	1.63	2.81
$t_{1/2}$ (hr)	4.32	4.08	5.35	7.71	13.61	6.99	18.22	15.7

Hepatic impairment

There are no data on the pharmacokinetics of amifampridine in patients with hepatic impairment (see sections 4.2 and 4.4).

Paediatric population

There are no data on the pharmacokinetics of amifampridine in paediatric patients (see sections 4.2).

The effect of age on the pharmacokinetics of amifampridine has not been studied.

5.3 Preclinical safety data

In safety pharmacology studies in rats, no respiratory system related effects were seen up to 10 mg/kg or on the central nervous system up to 40 mg/kg.

In a repeat-dose toxicity studies in rats and dogs, effects on the central and autonomic nervous system, increased liver and kidney weights and cardiac effects (second degree atrioventricular block) were seen. No safety margins to human exposure were achieved in the animal studies due to the sensitivity of the animal models used.

In a 2-year rat dietary carcinogenicity study, amifampridine caused small but statistically significant dose-related increases in the incidence of Schwannomas in both genders and of endometrial carcinomas in females. The clinical relevance of these results is unknown

Amifampridine was not genotoxic in a standard battery of *in vitro* and *in vivo* tests.

Animal studies evaluating the reproductive and developmental toxicity of amifampridine were conducted in rats and rabbits at doses up to 75 mg/kg/day. Amifampridine had no adverse reaction on male or female fertility in rats at doses up to 75 mg/kg/day, and no effect on post-natal development or fertility was observed in the offspring of the treated animals. In a perinatal/postnatal reproduction study in pregnant rats treated with amifampridine, a dose-related increase in the percentage of mothers with stillborn offspring (16.7%-20%) was observed at 22.5 mg/kg/day and 75 mg/kg/day (1.1 and 2.7 times the 80 mg per day dose in humans based on C_{max}). However, in a similar study in pregnant rabbits, there was no effect on embryo-foetal viability when evaluated just prior to birth at doses up to 57 mg/kg/day.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose
Calcium stearate
Anhydrous colloidal silica

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials

6.4 Special precautions for storage

Do not store above 25°C. Store in the original package in order to protect from light and moisture.

6.5 Nature and contents of container

Perforated unit dose thermoformed blisters (Thermoformed aluminium-PVC/PVDC laminate sheets) containing 10 tablets.

One box contains 100 tablets comprising 10 strips with 10 tablets each.

6.6 Special precautions for disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MANUFACTURER

SERB S.A.
Avenue Louise 480

1050 Brussels
Belgium

8. LICENSE HOLDER:

Medison Pharma Ltd.
10 Hashiloach Street
POB 7090
Petach Tikva, Israel

Registration Number:146-29-33301-01

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